REMARKS

Statement Of The Substance Of The Interview

Applicants thank Examiner Steele for the helpful interview at the United States Patent and Trademark Office ("USPTO") on October 8, 2008 ("Interview") with Applicants' representatives, Jacqueline Benn and Tracy LaGrassa, during which the pending rejections under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 103 were discussed.

Entry of this Statement Of The Substance Of The Interview into the file of this application is respectfully requested.

Statement Under 37 C.F.R. § 3.73(b) And Terminal Disclaimer

At the Interview, Examiner Steele informed representatives of the Applicants that the Terminal Disclaimers submitted on August 15, 2008 in view of U.S. Application No. 11/472,215 and U.S. Patent No. 5,876,727 is disapproved. Applicants note that the USPTO database also indicates that the Terminal Disclaimers submitted on August 15, 2008 is disapproved. As the Terminal Disclaimer has not been accepted, Applicants request that it be removed from the record.

Priority

Applicants acknowledge the Examiner's statement of the priority of the application. As amended, the limitations of nicotine derivatives, CJ 1.3, and CJ 11 in pending claims 125-126, 128, 131-138 and 141-142 are entitled to a priority date of September 30, 1996, *i.e.*, the filing date of U.S. Application No. 08/720,487, now U.S. Patent No. 5,876,727.

Claims

Upon entry of this amendment, claims 125-126, 128, 131-138 and 141-142 are pending in the present application. Claim 125 has been amended to recite a pharmaceutical composition comprising the hapten-carrier conjugate, to recite that Q is selected from elements of a Markush group, and to recite that the hapten-carrier conjugate is capable of eliciting an antibody response against nicotine in a human. Dependent claims 128, 131-138, and 142 have been amended so that they have proper antecedent basis in amended claim 125. Support for these amendments may be found in the specification at filed at *inter alia* page 10, lines 26-35; page 11, lines 4-8; and page 24, lines 19-23. No new matter has been added.

Withdrawn Objection and Rejections

Applicants acknowledge the withdrawal by the Examiner of the objection to claims 125, 126, 128, 129, and 131-140 regarding Markush groups.

Applicants acknowledge with appreciation the Examiner's withdrawal of the rejections of claims 125, 126, 128, 129, and 131-140 under 35 U.S.C. § 112, first paragraph.

Applicants acknowledge the Examiner's withdrawal of the rejections of claims 125, 126, 128, 129, and 131-140 under 35 U.S.C. § 103(a) over Walling et al., U.S. Patent No. 5,164,504 and Glenn et al., U.S. Patent No. 5,980,898, and, with respect to claims 133-135, further in view of Layton *et al.*

Claim Rejections Under 35 U.S.C. § 112, 2nd Paragraph

The Examiner has rejected claims 125-126, 128, 131, 138, and 141-142 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Applicants note that claim 140 has been canceled without prejudice.

Claim 125 has been amended to recite a pharmaceutical composition comprising the hapten-carrier conjugate, to recite that Q is selected from elements of a Markush group, and to recite that the hapten-carrier conjugate is capable of eliciting an antibody response against nicotine in a human. Dependent claims 128, 131-138, 141, and 142 have been amended so that they have proper antecedent basis in amended claim 125. Support for these amendments may be found in the specification at filed at *inter alia* page 10, lines 26-35; page 11, lines 4-8; and page 24, lines 19-23. Applicants believe that the amendments to claim 125 and its dependant claims obviate the rejections under 35 U.S.C. § 103 and 35 U.S.C. § 112, second paragraph.

Claim 142 is further rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for reciting the term "the hapten carrier," and thus lacking antedecedent basis. Claim 142 has been amended to delete the term "the hapten carrier" and to depend from claim 125, with proper antecedent basis.

Therefore, Applicants respectfully request the withdrawal of the rejections of claims 125, 126, 128, 131-138, and 142 under 35 U.S.C. § 112, second paragraph.

Response To Claim Rejections Under 35 U.S.C. § 103(a) For Obviousness Over Walling And Vyas

I. The claimed invention is not suggested by the cited art

The Examiner has rejected claims 125, 126, 128, 131-138, 141, and 142 under 35 U.S.C. §103(a) for alleged obviousness over the combination of Walling (U.S. Patent No.

5,164,504, issued November 17, 1992) and Vyas (U.S. Patent No. 4,483,793, issued November 20, 1984). The claimed invention is not obvious over the cited art because, alone or in combination, the cited art fails to suggest all the claim limitations. The claims as amended recite pharmaceutical compositions comprising nicotine or its derivatives coupled via a linker to a pseudomonas exotoxin carrier and wherein said hapten-carrier conjugate is capable of eliciting an antibody response against nicotine in a human.

In its recent decision addressing the issue of obviousness, *KSR Int'l. Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 U.S.P.Q.2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 U.S.P.Q. at 467; *see also*, Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* ("Examination Guidelines"), Federal Register, Vol. 72, No. 195, October 10, 2007, pages 57527-28. The Supreme Court stated that in determining obviousness, "a court must ask whether the improvement is more than a predictable use of prior art elements according to their established functions." *KSR*, 127 S.Ct. at 1740, 82 U.S.P.Q.2d at 1396. The Supreme Court also stated that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...." *KSR*, 127 S.Ct. at 1741, 82 U.S.P.Q.2d at 1396.

Walling not only fails to suggest the claimed invention, but in fact teaches away from the claimed invention. Walling describes cotinine, a nicotine metabolite, as a hapten coupled to a carrier such as bovine serum albumin (BSA), used to raise *cotinine-specific* antibodies in experimental animals (*e.g.*, mice) for use in immunoassays. *See*, *e.g.*, Walling, col. 1, lines 1-15 and 26-42; col. 5, lines 56-68; col. 6, lines 22-27; col. 7, lines 12-22; col. 17, lines 42 to col. 19, line 39. By contrast, the claimed invention relates to a pharmaceutical composition comprising a hapten-carrier conjugate wherein the hapten is a nicotine or nicotine derivative and the carrier is a bacterial toxin or sub-viral component, and wherein the hapten-carrier conjugate is capable of eliciting an antibody response against nicotine. Moreover, the specification of the claimed invention discloses that BSA, the carrier taught in Walling, would be an undesirable carrier because, as a food protein, it is present in beef consumed by humans and therefore, would fail to induce an immune response in humans because many

humans would be tolerant. *See*, page 29, lines 9-12. Therefore, Walling does not suggest a pharmaceutical composition comprising a hapten-carrier conjugate wherein the hapten is a nicotine or nicotine derivative and the carrier is a bacterial toxin or sub-viral component, and wherein the hapten-carrier conjugate induces a *nicotine-specific* antibody response in a subject. Indeed, Walling even teaches away from the claimed invention because Walling points to the advantages of raising antibodies that detect cotinine, not nicotine, due to its much longer half-life than nicotine and the ease of detection of cotinine compared to nicotine. *See*, Walling, at col. 1, lines 28-35.

As of the instant invention's filing date, not only Walling, but the art as a whole taught away from using nicotine-carrier conjugates for inducing an antibody response against nicotine in a human subject. As explained in the instant specification, nicotine is a small molecule hapten that is non-immunogenic, making it unlikely that one of skill in the art would expect to be able to successfully use it in a pharmaceutical composition capable of eliciting an immune response in a human. Not only is nicotine non-immunogenic, it actually – and in contrast to cotinine – *suppresses* the immune response. Geng *et al.*, "Effects of Nicotine on the Immune Response. I. Chronic Exposure to Nicotine Impairs Antigen Receptor-Mediated Signal Transduction in Lymphocytes," Toxicol. Appl. Pharmacol. 135: 268-78 (1995) (reference C93 of the Supplemental IDS, submitted concurrently herewith). *See, e.g.,* Abstract and Discussion section at page 75, 3rd paragraph. Because of its immunosuppressive effects, the skilled artisan would have had even more reason to doubt that nicotine and nicotine derivatives could be used in a pharmaceutical composition comprising a hapten-carrier conjugate wherein the hapten is a nicotine or nicotine derivative and the carrier is a bacterial toxin or sub-viral component, and wherein the hapten-carrier conjugate is capable of eliciting an antibody response against nicotine in a human.

Therefore, Walling's disclosure of cotinine-BSA for the purpose of raising cotinine-specific antibodies in animals, alone and in view of the art, does not suggest to the skilled artisan a viable approach for inducing antibodies against nicotine in human subjects.

Walling does not teach or suggest the use of a bacterial toxin as a carrier. The Examiner attempts to overcome this omission by citing Vyas. Vyas teaches the use of peptides from hepatitis B virus (HBV) surface antigen (HBsAg) to induce an immune response in a host in order to mimic the immune response that occurs during a natural HBV infection. *See*, Vyas at col. 1, lines 9-37; and col. 2, lines 8-19. In order to enhance the immune response to HBsAg peptides, Vyas suggests either oligomerizing the peptide or associating it with an adjuvant, *e.g.*, by conjugating it to a bacterial toxin against which the

host has been pre-immunized. *See*, Vyas at col. 3, lines 41-44; col. 6, lines 10-12 and 43-52; and col. 7, Table and lines 42-44.

The conjugates of Vyas are distinct from the hapten-carrier conjugates of the instant invention. While the presently claimed invention is drawn to nicotine (*i.e.*, a non-immunogenic, even immunosuppressive, hapten) conjugated to a bacterial toxin, Vyas only teaches using bacterial toxins as adjuvants for raising antibodies to Hepatitis B Antigen, an already *highly* immunogenic peptide. *See*, Abstract of Dietzman *et al.*, "Hepatitis B Surface Antigen (HB_sAg) and Antibody to HB_sAg," JAMA 238:2625-26 (1977) (C91 of the Supplemental IDS, submitted concurrently herewith). By contrast, nicotine is non-immunogenic and indeed has been shown to be immunosuppressive. Therefore, the conjugates of Vyas are distinct from the hapten-carrier conjugates of the instant invention.

Furthermore, the skilled artisan at the instant filing date would have recognized that there were contradictory teachings in the art with regard to the efficacy of using bacterial toxins as carriers to induce an antibody response *in humans*. Vyas teaches that bacterial toxins, such as tetanus toxoid or diphtheria toxoid are ideal for enhancing immunity to HBsAg peptides, *in an animal model*, such as rabbits, pre-immunized with tetanus toxin. *See*, Vyas, col. 5, lines 43-46; col. 6, line 54 to col. 7, line 33; and col. 7, lines 39-45. One of skill in the art would not have expected to successfully extend the teachings of Vyas to humans, however, because it was recognized in the art that prior exposure is a deterrent to using such bacterial toxins as an immunogen in humans. Prior exposure is an issue because (i) many humans are likely to have been previously infected with bacteria commonly used as sources for toxins and (ii) repeated immunizations, *e.g.*, a vaccine, might not have the necessary booster effect. For example, Schutze *et al.*, "Carrier-induced epitopic suppression, a major issue for future synthetic vaccines," J. Immunol. 135:2319-22 (1985) (reference C107 of the Supplemental IDS, submitted concurrently herewith) reported that the immune response against tetanus toxin-conjugates could be *suppressed* by pre-existing immunity to the toxin.

Thus, neither Walling nor Vyas, alone or combined, describes a composition comprising nicotine and pseudamonas exotoxin capable of eliciting a nicotine-specific antibody response in humans. Moreover, neither Walling nor Vyas, alone or combined, describes a hapten-carrier conjugate appropriate for administration in a human.

The claimed invention is not rendered obvious by the cited art, in part, because the cited art, taken alone or in combination, fails to describe or suggest all of the claim limitations. *Graham*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). Thus, the Examiner has failed to

establish a case of *prima facie* obviousness. However, assuming *arguendo*, that a *prima facie* case of obviousness has been made, the Applicants invite the Examiner's attention to the unexpected advantageous and/or superior properties associated with the claimed conjugates. (A *prima facie* case of obviousness is rebuttable by proof that the claimed compounds possess unexpectedly advantageous or superior properties. *In re Chupp*, 816 F.2d 643, 646; 2 U.S.P.Q.2d 1437, 1439 (Fed Cir 1987)). NicVAX is an example of a nicotine-pseudomonas exotoxin conjugate formulated as an anti-nicotine vaccine that is currently in clinical trials for smoking cessation in humans.

The Phase II clinical trials for NicVAX show that the nicotine-pseudomonas exotocin conjugate vaccine induces a nicotine-specific antibody response. *See*, Hatsukami *et al.*, "Safety and Immunogenicity of a Nicotine Conjugate Vaccine in Current Smokers" Clin. Pharmacol. Ther. 76: 456-67 (2005) (reference C82 of the Supplemental IDS filed June 12, 2008). The trials show a clear dose response relationship between dose of nicotine conjugate vaccine and mean concentration of nicotine-specific antibodies in serum. *See*, Hatsukami *et al.*, at page 464, right col., first full paragraph, and Figures 1 and 3. This study demonstrated that 6 out of 16 patients who received the vaccine at a dose of 200 μg were able to abstain from smoking cigarettes for at least 30 days during the study, as compared to 2 out of 23 patients that received placebo. These clinical trial results indicate that nicotine conjugated to a pseudomonas exotoxin carrier can be used efficaciously as a vaccine to elicit an antibody response to nicotine to treat nicotine addiction. Thus, these clinical trial results support the unexpected advantageous properties associated with the claimed conjugates.

Accordingly, reconsideration and withdrawal of the rejection of claims 88, 90, 103, 106, 108, 109, and 128-135 under 35 U.S.C. § 103(a) as being obvious over Walling and Vyas is respectfully requested.

Accordingly, reconsideration and withdrawal of the rejection of claims 125, 126, 128, 131-138, 141, and 142 under 35 U.S.C. § 103(a) as being obvious over Walling and Vyas is respectfully requested.

Double Patenting

Applicants have requested that the disapproved Terminal Disclaimers in view of U.S. Patent No. 5,876,727 (the "'727 patent") and co-pending application U.S. Application No. 11/472,215 (the "'215 application") be removed from the record. Further, in view of the amendments to the pending claims, Applicants submit that the double patent rejection in view of the '727 patent be withdrawn.

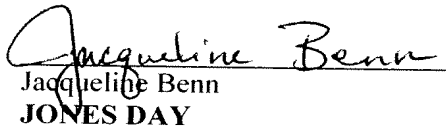
The M.P.E.P. states that "if a 'provisional' nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw the rejection and permit the earlier-filed appplication to issue as a patent without a terminal disclaimer." M.P.E.P. § 804I(B)(1). Accordingly, the instant application, filed August 22, 2003, was filed earlier than the '215 application, filed September 17, 2008, and therefore, should be allowed to issue at this time. Thus, in view of the amendments to the pending claims, Applicants submit that the double patent rejection in view of the '215 application should not apply.

CONCLUSION

Applicants respectfully request that the Examiner consider the amendments and the remarks made herein, and that the Examiner enter them into the record for the present application. Withdrawal of all rejections and an allowance is earnestly sought. The Examiner is invited to contact the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

Date: January 26, 2009



43,492
(Reg. No.)

Jacqueline Benn
JONES DAY
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939